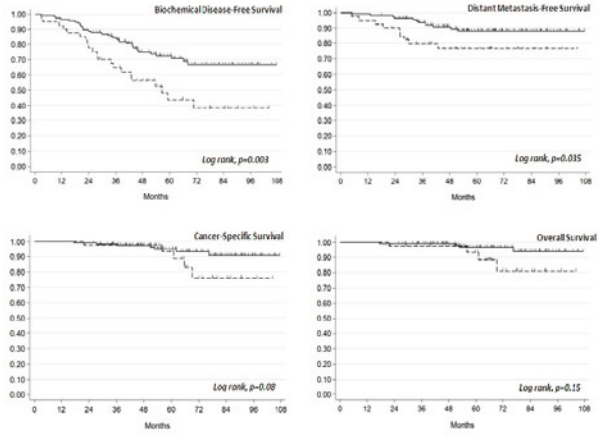
Materials and Methods: From 1993 to 2007, 953 patients (median age 65 years) underwent ADV (n=685) or SALV (n=268) RT with non conformal (n=169), 3DCRT (n=658) or IMRT (n=20) technique at 1.80 Gy/fraction, at a median RT dose of 70.2 Gy, or moderately hypofractionated (median 28 fractions) Tomotherapy (n=106) to a median 2-Gy equivalent (EQD2, a/b=3) dose of 70 Gy. WPRT was delivered to 282 patients at a median of 50 Gy. The median follow-up (FU) of pts treated with prostatic bed (PB) only RT was longer (110 *vs* 85 months) as compared to the WPRT+PB group.
Results: After a median FU of 103 months, actuarial 10-year overall survival (OS) was 86%. A 2ndNPL arose in 101 patients after a median of 46 months from RT (44/101 after >5 years). Thirty-two were INFIELD and 69 were OUTFIELD. The 10-year overall risk of 2ndNPL was 14% *vs* 9% (p=0.10) for pts receiving PB only or WPRT+PB, respectively (4% *vs* 2%, p=0.17, for INFIELD and 9% *vs* 6%, p=0.33, for OUTFIELD). Of note, the 10-year risk of 2ndNPL was significantly higher (17% *vs* 11%, p=0.02) in patients experiencing any (acute or late) GU toxicity Grade ≥2. Multivariate analysis, which indicated the independent predictive role of age >65 year in all subgroups, confirmed Grade ≥2 GU toxicity as a significant predictor of the risk of overall (HR 2.15, p=0.04) and OUTFIELD (HR 2.10, p=0.04), but not INFIELD 2ndNPL. When the analysis was limited to 2ndNPL onset after >5 year from RT, diabetes emerged as the only independent predictor of overall 2ndNPL (HR 2.19, p=0.048) and age >65 that of OUTFIELD ones (HR 1.08, p=0.02), while no factors independently predicted INFIELD 2ndNPL (n=13). Overall, 123 pts died, 53 owing to PCa progression, 34 to a 2ndNPL and 36 to non neoplastic causes. The 10-year risk of death was quite similar in pts experiencing a clinical relapse of PCa or an INFIELD or OUTFIELD 2ndNPL (40% vs 31% *vs* 37%, respectively, p=0.48) and significantly higher than that (6%) of pts bNEDs or with a PSA failure only after RT. Importantly, no role emerged for RT dose, technique or fractionation.
Conclusions: Although preliminary, this study suggests that the impact of treating larger volumes with WPRT may be not significant, in contrast with the hypothesis of a proportionally higher incidence of 2ndNPL with the increase of body integral dose. The correlation which emerged between GU toxicity and the risk of 2ndNPL deserves further investigation.

PD-0463
Radical radiotherapy in high-risk prostate cancer patients with high or ultra-high initial PSA levels.
A. Botticella[1], A. Guarneri[1], N. Giaj Levra[1], A.R. Filippi[1], F. Munoz[1], R. Ragona[1], U. Ricardi[1]
[1]*University of Torino, Radiation Oncology, Torino, Italy*

Purpose/Objective: Purpose of this study is to analyze outcomes and pre-treatment prognostic factors in high-risk prostate cancer patients with initial PSA ≥ 20 ng/mL, treated with high-dose External-Beam Radiotherapy (EBRT) and androgen-deprivation therapy (ADT) in a single institution.
Materials and Methods: Between March 2003 and December 2011, 155 consecutive high-risk prostate cancer patients a) presenting with pretreatment PSA level ≥ 20 ng/mL, b) treated with definitive EBRT and c) with a minimum follow-up of 24 months were included in this retrospective analysis. Phoenix definition was used to define biochemical control. Multivariate analysis was performed to determine the independent prognostic impact of pre-treatment clinical factors (T stage, PSA and Gleason Score [GS]) on clinical outcomes (biochemical Disease-Free Survival [bDFS], Distant Metastasis Free Survival [DMFS], Cancer-Specific Survival [CSS], Overall Survival [OS]).
Results:



	Biochemical DFS		DMFS		CSS		OS	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
PSA	0.003	0.027 (HR: 1.8)	0.03	NS	NS	NS	NS	NS
Gleason Score	0.003	0.022 (HR: 1.6)	NS	NS	0.05	0.044 (HR: 4.2)	NS	0.038 (HR: 2.6)
T stage	NS	NS	NS	NS	NS	NS	NS	NS

Table 1. Univariate and Multivariate analysis (Biochemical Disease Free Survival, bDFS; Distant Metastasis Free Survival, DMFS; Cancer Specific Survival, CSS; Overall Survival, OS)

At a median follow-up of 62 months, actuarial bDFS, DMFS, CSS and OS at 5 years were 64.8%, 85.2%, 95.8%, and 94.4%, respectively. On multivariate analysis, only GS was significantly associated with three clinical endpoints (bDFS: HR 1.6; *p=0.022*, CSS: HR 4.27, *p=0.044*, OS: HR 2.6;*p=0.038*). Pre-treatment zenith PSA (zPSA) was associated only with bDFS (HR 1.87; *p=0.027*).
Conclusions: Patients with 'high' PSAl evels (≥20 ng/mL) or 'ultra-high' PSA levels (≥ 50 ng/mL) showed favorable clinical outcomes, supporting thus the role of local radiotherapy as primary therapy in combination with long-term ADT in patients with high PSA levels at diagnosis. As GS of 8-10 resulted to be the strongest predictor of outcome, a subgroup of patients at worse prognosis might be early identified, since these patients represent the ideal candidates for more tailored and aggressive therapies in future trials.

PD-0464
Assessing response to chemotherapy with diffusion weighted MRI (DW-MRI) in muscle invasive bladder cancer (MIBC)
S. Hafeez[1], M. Koh[2], A. Sohaib[2], R. Huddart[1]
[1]*Royal Marsden Hospital, Academic Urology Unit, London, United Kingdom*
[2]*Royal Marsden Hospital, Radiology, London, United Kingdom*

Purpose/Objective: Neo-adjuvant chemotherapy (nCT) has known survival benefit in the treatment of MIBC. Favourable response is associated with improved outcome and identifies those who may benefit from bladder preservation with radical radiotherapy. Conventionally response assessment is with cystoscopy. We report on the use of DW-MRI as a potential non-invasive alternative means of assessment and as a predictor of nCT sensitivity.
Materials and Methods: 19 patients with confirmed MIBC suitable for nCT were recruited prospectively to an ethics approved protocol. DW-MRI was performed on a 1.5T system using b-values 0,50,100,250,500 and 750s/mm^2 prior to and on completion of nCT. Tumour was drawn on the 750s/mm^2 image and transferred onto the corresponding ADC map to record mean values. Following final DW-MRI patients proceeded to cystoscopy ± biopsy. Association between nCT sensitivity, pre-treatment ADC, post-treatment ADC and change of ADC (ΔADC) was analysed.
Results: 12 patients achieved pathological complete response, 6 achieved partial response and 1 progressed following nCT (as assessed on cystoscopy and T2-weighted MRI). In 15 patients tumour was identified on pre-nCT DW-image. 4 patients had no measurable disease on pre-nCT MRI. Baseline tumour median ADC was 1.3x10^{-3}mm^2/s (range 0.7-2.7x10^{-3}mm^2/s).
Complete response was associated with a significant increase in median ADC from 1.3x10^{-3}mm^2/s (range 0.7-2.7x10^{-3}mm^2/s) to 2.2x10^{-3}mm^2/s (range 1.9-3.2x10^{-3}mm^2/s) (p=0.036). Change in mean ΔADC was significantly greater in complete responders compared to incomplete responders; responders median ΔADC 1.1x10^{-3} mm^2/s, range 0.6-1.41x10^{-3}mm^2/s; incomplete responders median ΔADC 0.1x10^{-3}mm^2/s, range 0.03-0.3x10^{-3}mm^2/s (p=0.034).
Pre-treatment ADC was not predictive of response to nCT.

Response (n)	Median ADC (x10^{-3} mm^2/s) (range)		
	Pre chemotherapy	Post chemotherapy	
Complete (9)	1.31 (0.68-2.69)	2.21 (1.89-3.18)	p=0.036
Partial (5)	1.43 (1.01-1.62)	1.37 (1.07-1.71)	p=0.35
Progression (1)	1.07	0.93	
	p=0.36	p=0.35	

Conclusions: DW-MRI is useful in assessing response in MIBC. It may be a potential biomarker for predicting nCT sensitivity and guide selection for bladder sparing approaches but further work is needed.

POSTER DISCUSSION: YOUNG SCIENTISTS 4: CNS, GYNEACOLOGY AND HAEMATOLOGY

PD-0465

The effects of glycolysis targeting on the radiation response of hypoxic cervix xenograft tumours

E. Leung[1], N. Chaudary[2], T. Kalliomaki[2], H. Mujcic[2], E. Moriyama[3], B. Wouters[2], B. Wilson[3], R. Hill[2], M. Milosevic[1]
[1]*Princess Margaret Hospital, Radiation Medicine Program, Toronto, Canada*
[2]*University of Toronto, Division of Applied Molecular Oncology, Toronto, Canada*
[3]*University of Toronto, Division of Biophysics and Bioimaging, Toronto, Canada*

Purpose/Objective: Cancer cells exhibit increased glucose metabolism through an upregulation of glycolysis. Increased glycolysis may occur in response to hypoxia or in an oxygen-independent manner as a result of altered gene expression, both mediated via the HIF-1 transcription factor. It has been shown that tumours with high levels of glycolysis, as indicated by high lactate concentration, are less responsive to radiotherapy. The goal of this pre-clinical study was to evaluate glycolytic targeting by HIF-1 inhibition as a strategy to enhance radiation response.
Materials and Methods: Cervix (ME180) and hypopharynx (FaDu) xenograft tumours were grown in the hind leg of nude mice. Mice were placed in an environmental chamber for exposure to different oxygen conditions (20% or 7% inspired oxygen concentration for 3 hours). HIF-1 inhibition was achieved by two methods: a doxycycline-inducible HIF-1 negative mutant and lentiviral transfection of the HIF-1 shRNA. Glycolysis was evaluated using ex-vivo quantitative bio-luminescence microscopy of lactate concentration and distribution in tumour cryosections. Tumour hypoxic fraction was measured using EF5 immunohistochemical staining. Growth delay of xenografts was studied following their irradiation with a single 20Gy fraction.
Results: In air-breathing (20% oxygen) conditions, HIF-1 knockdown caused no significant difference in average lactate or EF5 levels or in tumour growth. Under conditions of hypoxia (7% oxygen), HIF-1 inhibition produced a significant ($p<0.05$) reduction in average lactate levels compared to controls in both the ME180 and FaDu tumours (15.8 to 12.4 µmol/g and 8.4 to 5 µmol/g respectively). The hypoxic fraction increased ($p<0.05$) with HIF-1 inhibition in both tumours (ME180: 0.09 to 0.13 and FaDu: 0.06 to 0.13). Tumours treated with a combination of HIF-1 knockdown and radiation had an increased growth delay compared to tumours treated with radiation alone ($p<0.05$). HIF-1 inhibition did not alter the growth of non-irradiated tumours.
Conclusions: HIF-1 inhibition can reduce glycolysis and improve radiation response in hypoxic tumours despite an associated increase in the hypoxic fraction. The underlying molecular mechanisms require further investigation but the results suggest that HIF-1 inhibitors, by virtue of their effects on tumour metabolism, might be useful radiosensitizing agents.

PD-0466

Apparent diffusion coefficient in carcinoma cervix: an imaging biomarker for radiation response.

R. Achari[1], S. Guha[1], A. Chandra[2], S. Sen[2], A. Mahata[1], S. Chatterjee[1], I. Mallick[1]
[1]*Tata Medical Center, Radiation Oncology, Kolkata, India*
[2]*Tata Medical Center, Diagnostic Radiology, Kolkata, India*

Purpose/Objective: Diffusion-weighted magnetic resonance imaging (DWI) provides information about the movement of water molecules inside tissue. The clinical utility of DWI in gynecologic malignancies has steadily increased over recent years. The purpose of our study is to focus on the quantitative index of DWI—the Apparent Diffusion Coefficient (ADC) value, to investigate its role as a predictor of treatment response and to establish a correlation between baseline ADC value and outcome.
Materials and Methods: A total of 20 patients (mean age 55.2 years) of squamous cell carcinoma cervix (FIGOStages IB through IIIB) who underwent radical chemoradiation and had a median follow up of 6 months were included in the ADC analysis. Apparent Diffusion Coefficient of ten normal controls was assessed. MRI was performed pretreatment and 3 months after treatment on a 3T Siemens MRI unit. For calculation of ADC a b value of 500mm^2/s was used. SPSS v 17.0 was used for analysis.
Results: The mean ADC of cervical carcinomas ($0.76 \pm 0.26 \times 10^{-3}$mm^2/s) was significantly lower than normal cervix ($1.45 \pm 0.46 \times 10^{-3}$mm^2/s) ($P<0.001$). The mean post treatment ADC values ($1.40 \pm 0.15 \times 10^{-3}$ mm^2/s) at 3 months were also significantly ($p<0.01$) higher in responders (n = 17) and they remain disease free at 6 months. Mean post treatment ADC values were $1.05 + 0.25 \times 10^{-3}$ mm^2/s at 3 months in nonresponders. However, there was no statistically significant correlation seen between pre treatment mean ADC and FIGO stage, nodal disease or tumour volume.
Conclusions: Baseline pretreatment ADC values are low in squamous cell carcinoma cervix and they show a significant change after radical chemoradiation in responders. Although our data is early and the patient numbers are small, there is indication that the absolute ADC value at 3 months post treatment can predict long term disease control and could help to identify a potential cut off value that may call for early clinical intervention in nonresponders.

PD-0467

Quality of life in women undergoing postoperative image guided intensity modulated radiation for cervical cancer.

S. Mohanty[1], S. Chopra[1], U. Mahantshetty[2], R. Engineer[2], S. Kannnan[3], B. Thomas[4], S.K. Shrivastava[2]
[1]*Tata Memorial Hospital and Advanced Centre for Treatment Research and Education in Cancer Tata Memorial Centre, Radiation oncology, Mumbai, India*
[2]*Tata Memorial Centre, Radiation oncology, Mumbai, India*
[3]*Advanced Centre for Treatment Research and Education in Cancer Tata Memorial Centre, Biostatistics, Mumbai, India*
[4]*Advanced Centre for Treatment Research and Education in Cancer Tata Memorial Centre, Research Nurse Radiation oncology, Mumbai, India*

Purpose/Objective: There is dearth of data on Quality of Life (QOL) in patients treated with Intensity Modulate Radiotherapy (IMRT) for cervical cancers. The present study was undertaken to quantify serial changes in QOL before and after postoperative IMRT.
Materials and Methods: Patients undergoing adjuvant or salvage IMRT (50 Gy/25 #/ 5 wks with concurrent weekly cisplatin and vaginal brachytherapy) within clinical trials completed the EORTC QLQC30 and cervix specific module (Cx-24) in EORTC validated vernacular language before, after, 3 and 6 months of completion of IMRT. Raw scores were calculated as per standard EORTC recommendations and final score was determined for each of the items using SPSS version 20.0. Wilcoxon signed rank test was applied for comparison between different time points at follow up. In subset analysis of 23 patients who completed 6 months follow up general linear model was used for within the subject analysis of variances (ANOVA). p value <0.05 was considered statistically significant.
Results: Forty patients undergoing adjuvant (n=26) and postoperative salvage (n=14) IMRT were included. At 3 months after completion of treatment, statistically significant improvement was observed across functional (except cognitive and social functioning) and symptom scales (except nausea and vomiting, dyspnoea, appetite loss and diarrhoea) when compared to pretreatment scores. Furthermore statistically significant improvement in global quality of life score (64.16 vs. 80.2,p=0.000). Amongst cervix specific QOL module (Cx-24) improvement in sexual and vaginal function was observed (85.93 vs. 71, p=0.02). The difference in all other organ specific functional scores was not significant. However in symptom scale, reduction in